

SUB
B4

WHAT IS CLAIMED IS:

1. A method for identifying a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

- (a) contacting an acid sphingomyelinase-deficient cell with a test compound;
 - (b) exposing the cell to a stress stimulus for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity;
 - (c) exposing an acid sphingomyelinase-deficient cell, in the absence of the test compound, to the stress stimulus for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity; and
 - (d) monitoring the exposed cells of steps (b) and (c) for the presence of an apoptotic morphology,
- such that if the cell from step (b) exhibits a more severe apoptotic morphology, than that of the cell from step (c) the test compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

2. A method for identifying a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

- (a) contacting an acid sphingomyelinase-deficient cell with a test compound;
- (b) exposing the cell to a stress stimulus;
- (c) exposing an acid sphingomyelinase-deficient cell, in the absence of the test compound, to the stress stimulus; and
- (d) comparing the levels of sphingomyelin and ceramide present in the exposed cell of step (b) to the levels present in the exposed cell of step (c),

such that if the level of sphingomyelin in the cell of step (b) is less than that of the cell of step (c), or the level of ceramide in the cell of step (b) is greater than that of the cell in step (c), the test compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

3. The method of Claim 1 or 2 wherein the cell is part of a genetically engineered nonhuman animal deficient for the acid sphingomyelinase gene.

4. A method for identifying a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

- 15 (a) contacting a cell exhibiting acid sphingomyelinase activity with a test compound;
- (b) exposing the cell to a stress stimulus;
- 20 (c) exposing a cell which exhibits acid sphingomyelinase activity to the stress stimulus, in the absence of the test compound; and
- (d) monitoring the exposed cells of steps (b) and (c) for the presence of an apoptotic morphology,
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such that if the cell from step (b) exhibits a less severe apoptotic morphology, than the cell from step (c) the test compound represents a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

30 5. A method for identifying a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

- 35 (a) contacting a cell exhibiting acid sphingomyelinase activity with a test compound;
- (b) exposing the cell to a stress stimulus;

(c) exposing a cell exhibiting acid sphingomyelinase activity to the stress stimulus, in the absence of the test compound; and

5 (d) comparing the levels of sphingomyelin and ceramide present in the exposed cell of step (b) to the levels present in the exposed cell of step (c).

such that if the level of sphingomyelin in the cell of step
10 (b) is greater than that of the cell of step (c), or the level of ceramide in the cell of step (b) is less than that of the cell in step (c), the test compound represents a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

15

6. The method of Claim 4 or 5 wherein the cell is a transgenic cell comprising a cell deficient in endogenous acid sphingomyelinase gene activity and containing a functional human acid sphingomyelinase transgene capable of
20 expressing functional human acid sphingomyelinase.

SUB B6
17. The method of Claim 6 wherein the cell is part of a genetically engineered nonhuman animal deficient in endogenous acid sphingomyelinase gene activity and containing
25 integrated in its cells a functional human acid sphingomyelinase transgene capable of expressing functional human acid sphingomyelinase.

SUB B7
8. The method of Claim 4 or 5 wherein the cell is a
30 genetically engineered cell which exhibits a greater level of acid sphingomyelinase activity than a non-genetically engineered cell of the same type.

add B8
19. The method of Claim 4 wherein the apoptotic
35 morphology comprises cellular condensation, nuclear condensation or zeiosis.